complex is specifically directed to hydroxymatairesinol (HMR) and a cyclodextrin.

The Patent Office concedes Ahotupa et al. fails to disclose an inclusion complex of HMR (Official Action, page 9, lines 3-4). Instead, the rejection was maintained based on Marfat et al. (Advisory Action, page 2, line 10 to page 3, line 4).

The Patent Office's reliance on Marfat et al. is misplaced because (1) it is directed to PD4E inhibitors, (2) it briefly mentions two lignans which act as PD4E inhibitors but which are structurally different from HMR, (3) it does not suggest the combination of HMR and cyclodextrin, and (4) one of ordinary skill in the art would not have a reasonable expectation of successfully complexing HMR with cyclodextrin from Marfat et al.:

1. Marfat et al. Is Not Directed to Lignan Compounds

Marfat et al. discloses thiazolyl-acid amide derivatives said to be useful as inhibitors of phosphodiesterase Type IV ("PDE4") isoenzymes. This lengthy reference (310 columns of text!) makes a brief reference to known lignan PD4E inhibitors T-440 and T-2585 (Col. 17, line 31 to Col. 18, line 20) before disclosing its thiazolyl-acid amide derivatives. The thrust of this reference is

not directed to lignan compounds but rather to its thiazolyl-acid amide derivatives of specified formula.

2. Marfat et al. Teaches the Combination of its Thiazolyl-Acid Amide Derivatives with Numerous Additives, Including Cyclodextrins

Marfat et al. does not disclose or suggest complexing lignans into cyclodextrins. Instead, Marfat et al. discloses numerous[1] possible additives for its thiazolyl-acid amide derivative composition. Even assuming, *arguendo*, one of ordinary skill would locate the cyclodextrin "tree" from this "forest" of additives *and* seek to complex a cyclodextrin with PD4E inhibitors *other than* Marfat et al.'s thiazolyl-acid amide derivatives, he would naturally use the T-440 and T-2585 compounds specifically disclosed by Marfat et al. *if* lignan PD4E inhibitors were chosen.

There is no teaching or suggestion in Marfat et al. to complex HMR with a cyclodextrin. It is respectfully submitted the Patent Office has impermissibly employed hindsight knowledge gleaned from the applicants' specification to supply a motivation or suggestion

[1]The additive list is exhaustive, and includes antimicrobial agents, antioxidants, buffering agents, chelating agents, dermatologically active agents, dispersing and suspending agents, emollients, emulsifying agents, excipients, sequestering agents such as cyclodextrins, solvents, and stabilizers. See Col. 258, line 16 to Col. 262, line 18.

absent from Marfat et al. to form a cyclodextrin inclusion complex of HMR.

3. T-440 and T-2858 Are Structurally Different From HMR

The two lignan compounds mentioned by Marfat et al. are structurally different from hydroxymatairesinol. Both T-440 and T-2585 have fused rings (See Col. 17, lines 30-49 of Marfat et al.), whereas HMR does not. Accordingly, T-440 and T-2585 can be expected to have a totally different degradation mechanism than HMR. Cyclodextrins should also have a different stabilizing effect on T-440 and T-2585 than HMR. The binding of a HMR formulation to receptors may also be different than the binding of a T-440 and T-2585-based cyclodextrin formulation.

4. Cyclodextrin Inclusion Complexes Require Experimentation

Not all compounds form cyclodextrin inclusion complexes, which follow the same principle as the ligand-receptor analogy in pharmacology. Small changes in guest molecule structure and even steric hindrance can alter the cyclodextrin's ability to form an inclusion complex.[2] Accordingly, one of ordinary skill in the art would not have a reasonable expectation of success that HMR would

[2]The importance of steric hindrance can be seen in the use of cyclodextrins to separate chiral enantiomers from one another.

form an inclusion complex with a cyclodextrin. Instead, laboratory testing has to be carried out in order to determine whether a compound will successfully form a cyclodextrin inclusion complex.

In short, one of ordinary skill in the art would not be motivated by Ahotupa et al. and Marfat et al. to form a cyclodextrin inclusion complex with HMR, and would not have a reasonable expectation HMR would form an inclusion complex with a cyclodextrin. Reconsideration and withdrawal of the obviousness rejection of claims 13-21 over Ahotupa et al. in view of Marfat et al. are earnestly requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of the rejection of claims 13-21, and issuance of a Notice of Allowance directed to those claims, are earnestly requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

The fees for an extension of time and a RCE are being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Supplemental Request.

Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

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Enclosures:
Petition for Extension of Time
Request for Continued Examination